Mechanisms associated with age and sex modulate motor-like tics via the CB₂ cannabinoid receptor

Presented By:
Sharon Anavi-Goffer, Dr (Ph.D.)
Δ⁹-THC, the psychoactive compound in cannabis, is a partial-agonist of CB₁ and CB₂ receptors

- Can the CB₂ receptor modulate motor tics?
- Is this mechanism associated with sex?
- Is this mechanism associated with age?

Gorberg et al., Br J Pharmacol. 2020
Gorberg et al., Mol Neurobiol. 2022
CB$_2$ receptor is expressed in the striatum and brainstem, where it regulates dopamine release:

- In adult male mice:
- JWH-133 (CB$_2$ receptor agonist) reduces adult locomotor activity.
- JWH-133 reduces cocaine-induced locomotor activity.
- HU-308 (5 mg/kg), CB$_2$ receptor agonist, reduces dyskinesia-like behavior in a model of Parkinson’s.

There is a complex mechanism for the control of motor activity by the CB$_2$ receptor:

- HU-308 (40 mg/kg, i.p.) has no effect on the locomotor activity of adult female mice.

Gorberg et al., Mol Neurobiol. 2022
From patients to animal models

Mechanisms of Dopaminergic and Serotonergic Neurotransmission in Tourette Syndrome: Clues from an in vivo Neurochemistry Study with PET

Dean F. Wong, James R. Brasic, Harvey S. Singer, David J. Schretlen, Hiroto Kuwabara, Yun Zhou, Ayon Nandi, Marika A. Maris, Mohab Alexander, Weiguo Ye, Olivier Roussel, Anil Kumar, Zsolt Szabo, Albert Gjedde, and Anthony A. Grace

Dopamine Pathways
- Functions
  - Reward (motivation)
  - Pleasure, euphoria
  - Motor function (fine-tuning)
  - Compulsion
  - Perseveration

Serotonin Pathways
- Functions
  - Mood
  - Memory processing
  - Sleep
  - Cognition

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Effects of $\Delta^9$-THC on DOI-induced tic-like behaviour of juvenile males

Central motor-like tic
HTR

Urge-like response
ESR

Caudally located motor-like tic
Grooming

- ~ 34% reduction of HTR
- Catalepsy at 5 mg/kg $\Delta^9$-THC

Gorberg et al., Br J Pharmacol. 2020

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**Δ⁹-THC: Decision making (Gorberg et al., Br J Pharmacol. 2020)**

**Juvenile mice**

- Caudally located motor-like tic
- Urge-like response

**Young adult mice**

- ID₅₀ 0.6 (0.2 - 2.4) mg/kg
- ID₅₀ 1.2 (0.3 - 7.6) mg/kg

% Grooming frequency above basal

% ESR frequency

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CBD increases motor-like tics

Juvenile mice

Young adult mice

![Graph showing the effect of CBD on HTR frequency in juvenile and young adult mice.](image)

**Gorberg et al., Br J Pharmacol. 2020**
CBD has no effect on DOI-induced motor-like tics in juvenile male mice

Central motor-like tic
HTR

Urge-like response
ESR

Peripheral motor-like tic
Grooming

Gorberg et al., Br J Pharmacol. 2020
Results with $\Delta^9$-THC and CBD are published

Gorberg V, McCaffery P, Anavi-Goffer S.

Different responses of repetitive behaviours in juvenile and young adult mice to $\Delta^9$-tetrahydrocannabinol and cannabidiol may affect decision making for Tourette syndrome.

Br J Pharmacol. 2020

This study was supported by a Research Grant Award from the Tourette Association of America
Objectives

Can the CB$_2$ receptor modulate motor tics?

1. What are the effects of HU-308, a selective CB$_2$ receptor agonist, on motor-like tics?

2. What are the effects on motor-like tics of HU-308 in the presence of DOI, a highly potent agonist of the serotonin 5-HT$_{2A/2C}$ receptors?

3. What are the effects of HU-308 on motor-like tics of CB$_2$ receptor knockout (CB$_2^{-/-}$) mice?

Gorberg et al., Mol Neurobiol. 2022
CB₂ receptor agonists increase motor-like tics in juvenile males

Gorberg et al., Mol Neurobiol. 2022
HU-308, a CB$_2$ receptor agonist, reduces locomotor activity in juvenile males

Gorberg et al., Mol Neurobiol. 2022
The increased HTR and ESR in juvenile mice that was induced by CB2 receptor agonists suggests that stimulation of the CB2 receptor may generate motor tics in children.

Gorberg et al., Mol Neurobiol. 2022
HU-308 has a lower or no effect on HTR in juvenile females

Juvenile males
- Vehicle + Saline n=7
- HU-308 0.2 mg/kg + Saline n=6
- HU-308 1 mg/kg + Saline n=7
- HU-308 5 mg/kg + Saline n=7

Juvenile females
- Vehicle + Saline n=6
- HU-308 0.2 mg/kg + Saline n=7
- HU-308 1 mg/kg + Saline n=7
- HU-308 5 mg/kg + Saline n=6

Gorberg et al., Mol Neurobiol. 2022
HU-308 significantly decreases basal grooming behavior in juvenile females but not in males

Gorberg et al., Mol Neurobiol. 2022
HU-308 (0.2 mg/kg) significantly inhibits DOI-induced motor-like tics in females but not in males.

Juvenile males

- Vehicle + Saline n=3
- Vehicle + DOI 1 mg/kg n=3
- HU-308 0.2 mg/kg + DOI 1 mg/kg n=5

Juvenile females

- Vehicle + Saline n=8
- Vehicle + DOI 1 mg/kg n=8
- HU-308 0.2 mg/kg + DOI 1 mg/kg n=8

Gorberg et al., Mol Neurobiol. 2022

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Conclusion & Implication

- HU-308 (0.2 mg/kg) significantly inhibits DOI-induced HTR and grooming behavior in females but not in males.

- The CB$_2$ receptor stimulation may possibly reduce the frequency of caudally located motor tics in girls.

- The CB$_2$ receptor contributes to the skewed ratio between boys and girls with Tourette syndrome, increasing the prevalence of Tourette syndrome in boys.

Gorberg et al., Mol Neurobiol. 2022
HU-308 (1, 5 mg/kg) reduces DOI-induced motor-like tics

**Juvenile males**

- Vehicle + Saline n=5
- vehicle + DOI 1 mg/kg n=5
- HU-308 1 mg/kg + DOI 1 mg/kg n=6
- HU-308 5 mg/kg + DOI 1 mg/kg n=5

**Juvenile females**

- Vehicle + Saline n=8
- Vehicle + DOI 1 mg/kg n=8
- HU-308 0.2 mg/kg + DOI 1 mg/kg n=8
- HU-308 1 mg/kg + DOI 1 mg/kg n=8
- HU-308 5 mg/kg + DOI 1 mg/kg n=8

Gorberg et al., Mol Neurobiol. 2022

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Conclusions & Implications

- CB₂ receptors modulate 5-HT\textsubscript{2A/2C}-induced motor tics in males and females
- The CB₂ receptor contributes to the skewed ratio between boys and girls with Tourette syndrome

Gorberg et al., Mol Neurobiol. 2022
Is this mechanism associated with age?

Age difference in the effect of HU-308 DOI-induced motor-like tics

Juvenile males

**Graph showing HTR frequency over time for different groups:**
- Vehicle+Saline n=5
- vehicle+DOI 1 mg/kg n=5
- HU-308 1 mg/kg + DOI 1 mg/kg n=6
- HU-308 5 mg/kg + DOI 1 mg/kg n=5

**Graph showing Grooming frequency over time for different groups:**
- Vehicle + Saline n=5
- Vehicle + DOI 1 mg/kg n=5
- HU-308 1 mg/kg + DOI 1 mg/kg n=6
- HU-308 5 mg/kg + DOI 1 mg/kg n=5

Young adult males

**Graph showing HTR frequency over time for different groups:**
- Vehicle + Saline n=3
- Vehicle + DOI 1 mg/kg n=3
- HU-308 0.2 mg/kg + DOI 1 mg/kg n=3
- HU-308 1 mg/kg + DOI 1 mg/kg n=3
- HU-308 5 mg/kg + DOI 1 mg/kg n=3

**Graph showing Grooming frequency over time for different groups:**
- Vehicle + Saline n=3
- Vehicle + DOI 1 mg/kg n=3
- HU-308 0.2 mg/kg + DOI 1 mg/kg n=3
- HU-308 1 mg/kg + DOI 1 mg/kg n=3
- HU-308 5 mg/kg + DOI 1 mg/kg n=3

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The CB$_2$ receptor mechanism that modulates 5-HT$_{2A/2C}$-induced motor-like tics is associated with age

Gorberg et al., Mol Neurobiol. 2022
The effects of HU-308 in adult male mice

Gorberg et al., Mol Neurobiol. 2022
The effects of HU-308 in adult female mice

**Adult females CB2<sup>-/-</sup> mice**

- Vehicle + DOI 1 mg/kg n=3
- HU-308 5 mg/kg + DOI 1 mg/kg n=4

**Adult females C57BL/6J mice**

- Vehicle + DOI 1 mg/kg n=3
- HU-308 5 mg/kg + DOI 1 mg/kg n=4

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Gorberg et al., Mol Neurobiol. 2022
Conclusion & Implications

HU-308 has an off-target effect which increases 5-HT$_{2A/2C}$-induced motor-like tics in adult female mice.

Discovering a new target that modulate motor tics will promote the development of new drugs.

Gorberg et al., Mol Neurobiol. 2022
A reduction in catabolic enzyme expression level will increase 2-AG and AEA levels.
PCR results DOI-induced motor tics

In left prefrontal cortex of juvenile male mice

CB₂ receptor

α/β-Hydrolase domain-containing 6 (ABHD6)

Fatty acid amide hydrolase (FAAH)

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A clinical study found increased 2-AG & AEA levels in the CSF of patients with TS.

Gorberg et al., Mol Neurobiol. 2022
Implications

- Correlating 2-AG levels from brain vs. CSF in animals vs. patients with Tourette syndrome
- Developing CB₂ receptor inhibitors to treat patients with Tourette syndrome

Gorberg et al., Mol Neurobiol. 2022
Gorberg V, Borisov V, Greig IR, Pertwee RG, McCaffery P, Anavi-Goffer S.

Motor-like Tics are Mediated by CB$_2$ Cannabinoid Receptor-dependent and Independent Mechanisms Associated with Age and Sex.


This study was supported by a Research Grant Award from the Tourette Association of America